PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/56, 31/435, 31/445

A1

(11) International Publication Number: **WO 98/25623**

(43) International Publication Date: 18 June 1998 (18.06.98)

(21) International Application Number: PCT/US97/22344

(22) International Filing Date: 5 December 1997 (05.12.97)

(30) Priority Data:

60/032,635	9 December 1996 (09.12.96)	US
9700221.6	8 January 1997 (08.01.97)	GB
60/047,174	20 May 1997 (20.05.97)	US

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: FUH, Vivian, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KAUFMAN, Keith, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WALDSTREICHER, Joanne [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING BONE LOSS

(57) Abstract

The present invention provides for a method of inhibiting bone loss in a subject in need of such treatment comprising administration of a therapeutically effective amount of the 5α–reductase type 2 inhibitor finasteride to the subject. The present invention further provides for a method for treating and preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, comprising administration of therapeutically effective amount of the 5α–reductase type 2 inhibitor finasteride to the subject. Further, the present invention provides for compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for inhibiting bone loss and treating or preventing osteoporosis and osteopenia.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE OF THE INVENTION
METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING BONE LOSS

FIELD OF THE INVENTION

The present invention provides for a novel method of preventing and/or treating bone loss. Further, the present invention is directed to methods of treating and/or preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The present invention also provides for a method of manufacture of a medicament useful for inhibiting bone loss, and for preventing and/or treating osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The present invention also provides for compositions useful in the methods of inhibiting bone loss and treating and/or preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

BACKGROUND OF THE INVENTION

The mechanism of bone loss is not well understood, but in practical effect, the disorder arises from an imbalance in the formation of new healthy bone and the resorption of old bone, with the result being a net loss of bone tissue. This bone loss includes a decrease in both mineral content and protein matrix components of the bone, and leads to an increased fracture rate of, predominantly, femoral bones and bones in the forearm and vertebrae. These fractures, in turn, lead to an increase in general morbidity, a marked loss of stature and mobility,

8/1/08, EAST Version: 2.2.1.0

and, in many cases, an increase in mortality resulting from complications.

Bone loss occurs in a wide range of subjects including aging men and women, post-menopausal women, patients who have undergone hysterectomy, patients who are undergoing or have undergone long-term administration of corticosteroids, patients suffering from Cushing's syndrome, and patents having gonadal dysgenesis.

Unchecked, bone loss can lead to osteoporosis and/or osteopenia. Osteopenia is reduced bone mass due to a decrease in the rate of osteoid synthesis to a level insufficient to compensate normal bone lysis. Osteoporosis is a major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume, producing porosity and fragility.

One on the most common types of osteoporosis is found in post-menopausal women affecting an estimated 20 to 25 million women in the United States alone. A significant feature of post-menopausal osteoporosis is the large and rapid loss of bone mass due to the cessation of estrogen production by the ovaries. Indeed, estrogens have been shown to limit the progression of osteoporotic bone loss, and estrogen replacement is a recognized treatment for postmenopausal osteoporosis in the United States and many other countries. Although the administration of estrogens have beneficial effects on bone when given even at very low levels, long-term estrogen therapy has been implicated in a variety of disorders such as an increase in the risk of uterine and breast cancer, vaginal bleeding, and endometrial hyperplasia, causing many women to avoid this treatment. Recently suggested therapeutic regimens which seek to lessen the cancer risk, such as administering combinations of progestogen and estrogen, may be linked to negative cardiovascular effects. Concerns over the significant undesirable effects associated with estrogen therapy, and the limited ability of estrogens to reverse existing bone loss, support the need to develop alternative therapy for bone loss that generates the desirable effects on bone but does not cause undesirable effects.

8/1/08, EAST Version: 2.2.1.0

Attempts to fill this need by the use of compounds commonly known as antiestrogens, which interact with the estrogen receptor, have had limited success, perhaps due to the fact that these compounds generally display a mixed agonist/antagonist effect. That is, although these compounds can antagonize estrogen interaction with the receptor, the compounds themselves may cause estrogenic responses in those tissues having estrogen receptors. Therefore, some antiestrogens, when administered alone, are subject to the same adverse effects associated with estrogen therapy.

Osteoporosis and osteopenia are present in both aging men and women, due to age-related bone loss.

Other treatments used for osteoporosis include vitamin and mineral supplementation with calcium and vitamin D. This has limited effectiveness in treating advanced disease and regular disease. The effectiveness of this treatment is limited in treating and preventing bone loss.

Treatment with bisphosphonates such as alendronate, currently marketed by Merck & Co., Inc. as FOSAMAX®, has also been successful in inhibiting bone loss and increasing bone density. Bisphosphonates have low bioavailability and their administration must avoid food interactions. Treatment with shots or intranasal Calcitonin and low dose PTH (parathyroid horomone) shots have also been employed in an effort to inhibit bone loss and treat or prevent osteoporosis. Treatment with calcitonin is associated with a high rate of allergic reaction.

Treatments used for bone loss in men include vitamin and mineral supplementation with calcium and vitamin D. This has limited effectiveness in treating advanced disease and regular disease. The effectiveness of this treatment is limited in treating and preventing bone loss.

Also, bone loss in men is treated with androgens such as testosterone. Treatment with testosterone can lead to baldness, acne, lowering of HDL cholesterol (the "good" cholesterol) and raising of LDL cholesteroal (the "bad" cholesterol), and it may be associated with an increased risk of prostate cancer and benign prostatic hyperplasia.

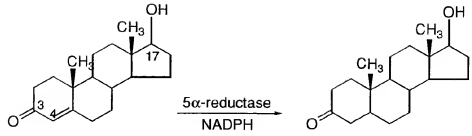
8/1/08, EAST Version: 2.2.1.0

U.S. 5,550,134, issued August 27, 1996, describes methods for inhibiting the loss of bone with benzoquinolin-3-ones known to be inhibitors of the enzyme 5α-reductase type 1. U.S. 5,550,134 describes that the type 1 isoform of the 5α-reductase enzyme is the form of the enzyme which is active in one of the processes which affect the formation/resorption of bone.

The present invention relates to methods of inhibiting bone loss without the associated adverse effects of hormone replacement therapy, and thus, serves as an effective acceptable treatment for osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. Surprisingly, it has now been found that a 5α-reductase type 2 inhibitor is useful for the inhibition of bone loss and the treatment of the associated clinical conditions. In particular, the present invention relates to the use of the 5α-reductase type 2 inhibitor finasteride for the inhibition of bone loss and the treatment and prevention of osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. The inhibition of bone loss contemplated by the present methods includes both medical therapeutic and/or prophylactic treatment, as appropriate.

The enzyme 5α-reductase catalyzes the reduction of testosterone (T) to the more potent androgen, 5α-dihydrotestosterone (dihydrotestosterone" or DHT), as shown below:

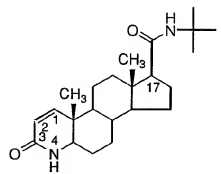
8/1/08, EAST Version: 2.2.1.0



testosterone dihydrotestosterone

There are two isozymes of 5α-reductase in humans. Andersson, et al., Proc. Natl. Acad. Sci. USA, 87:3640-44 (1990); Andersson, et al., Nature, 354, 159-61 (1991). The isozymes, usually called Type 1 and Type 2, exhibit differences in their biochemical properties, genetics, and pharmacology. Both isozymes are now the subject of considerable research and it has been found one isozyme (type 1) predominates in the sebaceous glands of facial skin and skin tissue and that the other (type 2) predominates in the prostate.

Finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) as shown below, is a potent inhibitor of the human type 2 enzyme.



finasteride

Under the tradename PROSCAR®, finasteride is known to be useful in the treatment of hyperandrogenic conditions, see e.g., U.S. 4,760,071.

8/1/08, EAST Version: 2.2.1.0

Finasteride is currently prescribed for the treatment of benign prostatic hyperplasia (BPH), a condition affecting to some degree the majority of men over age 55. Finasteride's usefulness in the treatment of androgenic alopecia and prostatic cancer is described in the following documents: EP 0 285 382, published 5 October 1988, EP 0 285 383, published 5 October 1988 and Canadian patents 1,302,277 and 1,302,276.

Finasteride has been reported to have no effect on bone density. Tollin et al. "Finasteride therapy does not alter bone turnover in men with benign prostatic hyperplasia--A clinical research center study" (J. Clin Endocrin. & Metab. 81(3):1031-1034, 1996), report that finasteride had no effect on bone and mineral metabolism. Matzkin et al. "Prolonged treatment with finasteride (a 5α-reductase inhibitor) does not affect bone density and metabolism" (Clin. Endocrin. 37:432-436, 1992) also conclude that in elderly men, finasteride had no effect on bone density or mineral metabolism except for an increase in serum 1,25-dihydroxy vitamin D. Rosen et al. "Bone density is normal in male rats treated with finasteride (Endocrinology 136(4):1381-1387, 1995) reported that bone development and density were normal in rats treated with finasteride.

SUMMARY OF THE INVENTION

The present invention provides for a method of inhibiting bone loss in a subject in need of such treatment comprising administration of a therapeutically effective amount of the 5α-reductase type 2 inhibitor finasteride to the subject. The present invention further provides for a method for treating and preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease as well as reducing the risk of fractures, both vertebral and nonvertebral, comprising administration of therapeutically effective amount of the 5α-reductase type 2 inhibitor finasteride to the subject. Further, the present invention provides for compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful

8/1/08, EAST Version: 2.2.1.0

for inhibiting bone loss and treating or preventing osteoporosis and osteopenia.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention is directed to a method for inhibiting bone loss in a subject in need thereof by administering an effective amount of a 5α-reductase type 2 inhibitor to the subject.

In one class of this embodiment, the present invention is directed to a method for inhibiting bone loss in a subject in need thereof by administering an effective amount of the 5α-reductase type 2 inhibitor finasteride to the subject.

Still a further aspect of the present invention is a method of preventing diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject in need thereof by administering an effective amount of the 5α-reductase type 2 inhibitor finasteride to the subject.

Still another aspect of the present invention is the method of reducing the risk of diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject at risk therefor by administering an effective amount of the 5α-reductase type 2 inhibitor finasteride to a subject.

Yet a further aspect of the present invention is the method of treating diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject in need thereof by

8/1/08, EAST Version: 2.2.1.0

administration of an effective amount of the 5α-reductase type 2 inhibitor finasteride to the subject.

Another aspect of the present invention is the use of the 5α-reductase type 2 inhibitor finasteride for the manufacture of a medicament useful to inhibit bone loss in a subject in need thereof. Still a further aspect of the present invention is the use of the 5α-reductase type 2 inhibitor finasteride for the manufacture of a medicament useful to prevent diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral. Still another aspect of the present invention is the use of the 5α-reductase type 2 inhibitor finasteride for the manufacture of a medicament useful to reduce the risk of diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral, in a subject at risk therefor. Yet a further aspect of the present invention is the use of the 5α-reductase type 2 inhibitor finasteride for the manufacture of a medicament useful to treat diseases of the bone where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

Also useful in the present invention are pharmaceutically acceptable salts of the 5α-reductase type 2 inhibitor finasteride.

The subject treated in the methods above is a mammal, preferably a human being, male or female, at risk of developing a disease where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

8/1/08, EAST Version: 2.2.1.0

Alternatively the subject treated is a mammal, or preferably a human being, who has developed a disease where inhibiting bone loss may be beneficial, including: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

A subject in need of the present invention may also be identified as possessing bone fractures.

The term "therapeutically effective amount" means the amount of 5α-reductase type 2 inhibitor finasteride that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The instant method of administering the 5α-reductase type 2 inhibitor finasteride is useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.

2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in

8/1/08, EAST Version: 2.2.1.0

bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany, as well as reducing the risk of fractures, both vertebral and nonvertebral.

The administration of finasteride in order to practice the present methods of therapy is carried out by administering an effective amount of finasteride to the patient in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment. It will be observed that finasteride is active at very low concentrations, and hence at low dosage levels, thereby allowing effective bone loss inhibition with slight probability of side effects or cross-reactions with other treatments or drugs.

Generally, the daily dosage of the 5α-reductase type 2 inhibitor finasteride may be varied over a wide range from 0.01 to 10 mg per adult human per day. In a preferred embodiment, finasteride is administered at a dose of 1 to 5 mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.02, 0.05, 0.1, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, and 10.0 milligrams of active ingredient for the symptomatic adjustment of the dosage to the subject to be treated.

8/1/08, EAST Version: 2.2.1.0

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, when administered via intranasal routes, transdermal routes, by rectal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Formulations of the 5α-reductase inhibitor employed in the present method for medical use comprise the 5α-reductase type 2 inhibitor finasteride together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient subject of the formulation.

The present invention, therefor further provides a pharmaceutical formulation comprising the 5α-reductase type 2 inhibitor finasteride together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, rectal, intravaginal, topical or parenteral (including subcutaneous, intramuscular and intravenous administration). Preferred are those suitable for oral administration.

The formulations may be presented in a unit dosage form and may be prepared by any of the methods known in the art of pharmacy. All methods include the step of bringing the active compound in association with a carrier which constitutes one or more ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound in association with a liquid carrier, a waxy solid carrier or a finely divided solid carrier, and then, if needed, shaping the product into desired dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or

8/1/08, EAST Version: 2.2.1.0

solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, or an emulsion.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents, disintegrating agents or coloring agents. Molded tablets may be made by molding in a suitable machine a mixture of the active compound, preferably in powdered form, with a suitable carrier. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral liquid forms, such as syrups or suspensions in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl cellulose and the like may be made by adding the active compound to the solution or suspension. Additional dispersing agents which may be employed include glycerin and the like.

Formulations for rectal administration may be presented as a suppository with a conventional carrier, i.e., a base that is nontoxic and nonirritating to mucous membranes, compatible with the 5α-reductase type 2 inhibitor finasteride, and is stable in storage and does not bind or interfere with the release of the finasteride. Suitable bases include: cocoa butter (theobroma oil), polyethylene glycols (such as carbowax and polyglycols), glycol-surfactant combinations, polyoxyl 40 stearate, polyoxyethylene sorbitan fatty acid esters (such as Tween, Myrj, and Arlacel), glycerinated gelatin, and hydrogenated vegetable oils. When glycerinated gelatin suppositories are used, a preservative such as methylparaben or propylparaben may be employed.

8/1/08, EAST Version: 2.2.1.0

Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations. See, e.g., EP 0 285 382.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamidephenol, or polyethylene-oxide polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Formulations suitable for parenteral administration include formulations which comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution or suspension of a compound that is isotonic with the blood of the recipient subject. Such formulations may contain distilled water, 5% dextrose in distilled water or saline and the active compound. Often it is useful to employ a pharmaceutically and pharmacologically acceptable acid addition salt of the active compound that has appropriate solubility for the solvents employed. Useful salts include the hydrochloride isothionate and

8/1/08, EAST Version: 2.2.1.0

methanesulfonate salts. Useful formulations also comprise concentrated solutions or solids comprising the active compound which on dilution with an appropriate solvent give a solution suitable for parenteral administration.

The compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance vitamin D_2 and D_3 and hydroxylated derivatives, e.g. 1α-hydroxy-vitamin D_3, 1α-hydroxy-vitamin D_2, 1α-25-dihydroxy-vitamin D_3, 1α-25-dihydroxy-vitamin D_2, dehydroepiandrosterone, calcitonin (human, porcine or salmon), mitramycin, sodium fluoride, estrogens, estrogen mimetics, including reloxafine and other compounds within the oxefine class, non-steroid antiinflammatory drugs, such as acetylsalicyclic acid, indomethacin, naprosyn, and timegadine, growth hormone secretagogues, growth hormone, growth hormone releasing hormone and insulin-like growth factor and bisphosphonates such as alendronate.

One aspect of the present invention provides a method for inhibiting bone loss comprising administering to a mammal in need of treatment an effective amount of the 5α-reductase type 2 inhibitor, finasteride.

Another aspect of the present invention provides the above-described method, and further comprises the coadministration of a bone antiresorptive agent and/or an anabolic agent. Bone antiresportive agents are those agents which are known in the art to inhibit the resorption of bone and include, for example, estrogen in which estrogen includes steroidal compounds having estrogenic activity such as, for

8/1/08, EAST Version: 2.2.1.0

example, 17β-estradiol, estrone, conjugated estrogen (PREMARIN®), equine estrogen, 17β-ethynyl estradiol, and the like.

Bisphosphonate compounds may also be employed in combination with the 5α-reductase type 2 inhibitor finasteride of the present invention include:

(a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,

(b) N-methyl-4-amino-hydroxybutylidene-1,1-bisphosphonic acid,

(c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-bisphosphonic acid,

(d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,

(e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid,

(f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid,

(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid, and

(h) 4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine,

and their pharmaceutically acceptable salts. Especially preferred are alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt, trihydrate. Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,077. In particular, methods for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Patent No. 4,407,761 and U.S. Patent No. 4,621,077.

Still further, antiestrogenic compounds such as raloxifene (see, e.g., U.S. Pat. No. 5,393,763) clomiphene, zuclomiphene, enclomiphene, nafoxidene, CI-680, CI-628, CN-55,945-27,Mer-25, U-11,

8/1/08, EAST Version: 2.2.1.0

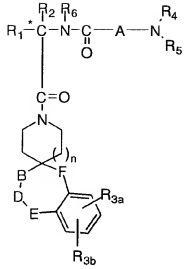
555A, U-100A, and salts thereof, and the like (see, e.g., U.S. Pat. Nos. 4,729,999 and 4,894,373) may be employed in combination with the 5α-reductase type 2 inhibitor finasteride in the methods and compositions of the present invention.

Bone anabolic agents are those agents which are known in the art to build bone by increasing the production of the bone protein matrix. Such anabolic agents include, for example, the various forms of parathyroid hormone (PTH) such as naturally occurring PTH (1-84), PTH (1-34), analogs thereof, growth hormone secretagogues, growth hormone, growth hormone releasing hormone and insulin-like growth factorand the like.

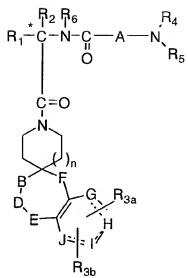
Representative growth hormone secretagogues are disclosed in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

Representative growth hormone secretagogues are disclosed in U.S. Patent No. 5,536,716 as spiro compounds of the following structural Formulas I and II:

8/1/08, EAST Version: 2.2.1.0



Formula I



Formula II

wherein the various substituents are as defined in U.S. Patent No. 5,536,716.

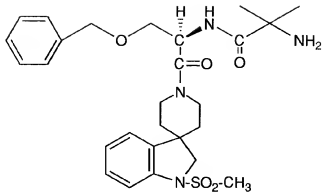
Preferred growth hormone secretagogues for use in the present invention include:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and

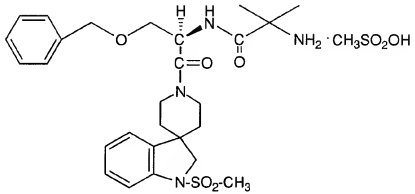
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

Especially preferred growth hormone secretagogues specifically include:

8/1/08, EAST Version: 2.2.1.0



and pharmaceutically acceptable salts thereof; and



The preparation of growth hormone secretagogues is well known in the literature. Full descriptions of the preparation of the growth hormone secretagoues is found in e.g., U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO

8/1/08, EAST Version: 2.2.1.0

95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

Daily dosage ranges for bone antiresorptive and anabolic agents are those which are known in the art.

In particular, when a bisphosphonic acid is employed, dosages of 2.5 to 100 mg/day (measured as the free acid) are appropriate for treatment, more preferably 5 to 20 mg/day, especially about 10 mg/day. Prophylactically, doses of about 2.5 to about 10 mg/day and especially about 5 mg/day should be employed.

The compounds of the methods of the present invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal, and such compounds are preferably formulated prior to administration. Therefore, another embodiment of the present invention is a pharmaceutical formulation comprising an effective amount of finasteride or a pharmaceutically acceptable salt thereof, a bone antiresorptive or anabolic agent, and a pharmaceutically acceptable carrier, diluent or excipient therefor.

In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating or preventing bone loss includes in principle any combination with any pharmaceutical composition useful for inhibiting bone loss or building new bone.

8/1/08, EAST Version: 2.2.1.0

The 5α-reductase type 2 inhibitor finasteride that is employed this invention can be prepared as described in U.S. 4,760,071.

The following examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Furthermore, examples are not to be construed as forming the only methods and compositions that are considered as the invention. Those skilled in the art will readily understand that known variations of the conditions, processes, methods and compositions of the following preparative procedures can be used.

EXAMPLE 1

Effect of the 5α-reductase type 2 inhibitor finasteride on bone mineral density in men

Sixty-three healthy, young men entered the study and were randomized to treatment with 1 mg/day finasteride or placebo for 48 weeks. The placebo group contained 29 men and the treatment group contained 34 men. Lumbar spine bone mineral density, measured by dual energy X-ray absorptiometry (DXA), and indices of bone metabolism, including Cross-Linked N-Telopeptides of Type 1 Collagen (NTX) measured in urine and serum Bone-Specific Alkaline Phosphatase (BSAP) were measured at weeks 12, 24, 36 and 48.

There was a trend for finasteride patients to have a small increase in lumbar spine bone mineral density of 0.7%, and for the placebo group to experience a small decrease of -0.2% (p= 0.08 difference between treatment groups).

For the marker of bone resorption (NTX), finasteride subjects showed a measurable reduction from baseline at Weeks 24, 26, and 48 of 29.6, 40.2, and 43.1% (median percent change), respectively, and the Week 48 result was significant compared with placebo, as shown in Table 1, below:

8/1/08, EAST Version: 2.2.1.0

Table 1: Median Analysis Results for Percent Change from Baseline to Week 48 in Cross-Linked N-Telopeptides of Type 1 Collagen (pmol bone collagen equivalent (BCE)/mL)

Finasteride, 1 mg (% change)	Placebo (% change)	Difference	95% Confidence Interval	p-Value
-43.1	-11.3	-28.3	(-50.1, -5.9)	0.020

Correcting the results above for creatinine levels, the following results were obtained as shown in Table 1A:

Table 1A: Median Analysis Results for Percent Change from Baseline to Week 48 in Cross-Linked N-Telopeptides of Type 1 Collagen corrected for urinary Creatinine Levels (nM BCE/mM creatinine)

Finasteride, 1 mg (% change)	Placebo (% change)	Difference	95% Confidence Interval	p-Value
-18.3	-9.9	-13.5	(-27.1, -0.3)	0.047

For the marker of bone formation, bone specific alkaline phosphatase (BSAP), a treatment group difference was detected at Week 48, but this was due to a rise of 14% (mean percent change) in the placebo subjects. The 4.4% increase in finasteride subjects was not significantly different from baseline, as shown in Table 2.

Table 2: ANOVA Results for Percent Change from Baseline to Week 48 in Bone Specific Alkaline Phosphatase (ng/mL)

Finasteride, 1 mg (% change)	Placebo (% change)	Difference	95% Confidence Interval	p-Value
4.4	14.0	-9.7	(-17.8,-1.5)	0.021

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 2

One-hundred-fifty older men with benign prostatic hyperplasia are enrolled as part of a large (3014 patients), 4-year, double-blind, placebo-controlled trial. Bone density is measured at baseline, years 2, 3, and 4. Biochemical markers of bone are also measured at these time points.

EXAMPLE 3

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 3 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 4

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 0.5 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 5

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 2.5 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 6

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 6 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 7

Transdermal Patch Formulation

Ingredient	Amount
finasteride	40 g
Silicone fluid	45 g
Colloidal silicone dioxide	2.5 g

The silicone fluid and finasteride are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut into 10 cm^2 patches. For 100 Patches.

EXAMPLE 8

Suppository

Ingredient	Amount
finasteride	25 g
Polyethylene glycol 1000	1481 g
Polyethylene glycol 4000	494 g

The polyethylene glycol 1000 and polyethylene glycol 4000 are mixed and melted. The finasteride is mixed into the molten mixture, poured into molds and allowed to cool. For 1000 suppositories.

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 9

Injectable solution

Ingredient	Amount
finasteride	5 g
Buffering agents	q.s.
Propylene glycol	400 mg
Water for injection	600 mL

The finasteride and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving. For 1000 Ampules.

EXAMPLE 10

Injectable solution

Ingredient	Amount
finasteride	5 g
Buffering agents	q.s.
Magnesium sulfate heptahydrate	100 mg
Water for injection	880 mL

The finasteride, magnesium sulfate heptahydrate and buffering agents are dissolved in the water for injection with stirring, and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving. For 1000 Ampules.

EXAMPLE 11

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 3 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) and 2.5 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 12

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 0.5 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) and 10.0 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate)is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 13

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 2.5 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) and 5.0 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate)is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

EXAMPLE 14

Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 6 mg of finasteride (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-en-3-one) and 2.5 mg of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 15

Transdermal Patch Formulation

Ingredient	Amount
alendronate	50 g
finasteride	40 g
Silicone fluid	45 g
Colloidal silicone dioxide	2.5 g

The silicone fluid alendronate and finasteride are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut into 10 cm^2 patches. For 100 Patches.

EXAMPLE 16

Preparation of Human Prostatic and Scalp 5α-Reductases

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500 x g for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

8/1/08, EAST Version: 2.2.1.0

EXAMPLE 17

5α-Reductase Assay

The reaction mixture for the type 1 5α-reductase contained 40 mM potassium phosphate, pH 6.5, 5 mM [7-^{3}H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μL. The reaction mixture for the type 2 5α-reductase contained 40 mM sodium citrate, pH 5.5, 0.3 mM [7-^{3}H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μL. Typically, the assay was initiated by the addition of 50-100 μg prostatic homogenate or 75-200 μg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 μL of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 μg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman Partisil 5 silica column equilibrated in 1 ml/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655α Autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Inhibition Studies

Compounds were dissolved in 100% ethanol. The compound to be tested was pre-incubated with the enzyme (either 5α-reductase type 1 or 2) prior to initiation by addition of substrate testosterone. IC_{50} values represent the concentration of inhibitor required to decrease enzyme conversion of testosterone to dihydrotestosterone by 50% of the control. IC_{50} values were determined using a 6 point titration where the concentration of the inhibitor was varied from 0.1 to 1000 nM.

8/1/08, EAST Version: 2.2.1.0

Representative compounds of this invention were tested in the above described assay for 5α-reductase type 1 and type 2 inhibition.

A compound referred to herein as a 5α-reductase 2 inhibitor is a compound that shows inhibition of the 5α-reductase 2 isozyme in the above-described assay, having an IC_{50} value of about or under 100 nM.

The compounds are tested in the above-described assay for 5α-reductase type 1 and type 2 inhibition, and were found to have IC_{50} values under about 100 nM for inhibition of the type 1 isozyme. Compounds found to have IC_{50} values of under about 50 nM for inhibition of the type 1 isozyme are called type 1 inhibitors. Compounds called "dual inhibitors" additionally had IC_{50}'s under about 200 nM for inhibition of the type 2 isozyme.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

8/1/08, EAST Version: 2.2.1.0

WHAT IS CLAIMED IS:

1. A method of inhibiting bone loss in a subject in need of such treatment comprising administration of an effective amount of the 5α-reductase type 2 inhibitor finasteride.

2. The method of Claim 1 wherein the subject is a mammal.

3. The method of Claim 2 wherein the subject is a human.

4. The method of Claim 1 wherein the finasteride is administered at a dose of 0.01 to 10 mg per day.

5. The method of Claim 4 wherein the finasteride is administered at a dose of 1 to 5 mg per day.

6. The method of inhibiting bone loss in a subject in need of such treatment according to Claim 1 comprising administration of an effective amount of the 5α-reductase type 2 inhibitor finasteride and an effective amount of a bone anabolic agent or a bone antiresorptive agent.

7. The method according to Claim 6 wherein the bone anabolic agent is selected from a form of parathyroid hormone and a growth hormone secretagogue, growth hormone, growth hormone releasing hormone and insulin-like growth factor.

8. The method according to Claim 7 wherein the growth hormone secretagogue is selected from:

(a) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and

8/1/08, EAST Version: 2.2.1.0

(b) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

9. The method according to Claim 6 wherein the bone antiresorptive agent is selected from:

(1) an estrogen,

(2) a bisphosphonate compound, and

(3) an antiestrogenic compound.

10. The method according to Claim 9 wherein:

(1) the estrogen is selected from:

(a) 17β-estradiol,

(b) estrone,

(c) conjugated estrogen, equine estrogen, and

(d) 17β-ethynyl estradiol;

(2) the bisphosphonate compound is selected from:

(a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,

(b) N-methyl-4-amino-hydroxybutylidene-1,1-bisphosphonic acid,

(c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-bisphosphonic acid,

(d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,

(e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid,

(f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid,

(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid, and

(h) 4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine; and

(3) the antiestrogenic compound is selected from:

(a) raloxifene,

(b) clomiphene,

8/1/08, EAST Version: 2.2.1.0

(c) zuclomiphene,
(d) enclomiphene,
(e) nafoxidene,
(f) CI-680,
(g) CI-628,
(h) CN-55,945-27,
(i) Mer-25,
(j) U-11,
(k) 555A, and
(l) U-100A;

and pharmaceutically acceptable salts thereof.

11. The method of inhibiting bone loss in a subject in need of such treatment according to Claim 10 comprising administration of 0.01 to 10 mg/day of the 5α-reductase type 2 inhibitor finasteride together with 2.5 to 100 mg/day of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

12. A method of treating and preventing a disease involving bone resorption selected from: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease which comprises the administration to a subject in need thereof of an effective amount of a the 5α-reductase type 2 inhibitor finasteride to the subject.

13. The method of Claim 11 wherein the subject is a human.

14. The method of Claim 12 wherein the finasteride is administered at a dose of 0.01 to 10 mg per day.

15. The method of Claim 14 wherein the finasteride is administered at a dose of 1 to 5 mg per day.

8/1/08, EAST Version: 2.2.1.0

16. The method of treating and preventing a disease involving bone resorption selected from: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease in a subject in need thereof according to Claim 12 comprising administration of an effective amount of the 5α-reductase type 2 inhibitor finasteride and an effective amount of a bone anabolic agent or a bone antiresorptive agent.

17. The method according to Claim 16 wherein the bone anabolic agent is selected from a form of parathyroid hormone and a growth hormone secretagogue, growth hormone, growth hormone releasing hormone and insulin-like growth factor.

18. The method according to Claim 17 wherein the growth hormone secretagogue is selected from:

(a) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide; and

(b) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate.

19. The method according to Claim 16 wherein the bone antiresorptive agent is selected from:

(1) an estrogen,

(2) a bisphosphonate compound, and

(3) an antiestrogenic compound.

20. The method according to Claim 19 wherein:

(1) the estrogen is selected from:

(a) 17β-estradiol,

(b) estrone,

(c) conjugated estrogen, equine estrogen, and

(d) 17β-ethynyl estradiol;

(2) the bisphosphonate compound is selected from:

8/1/08, EAST Version: 2.2.1.0

(a) 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid,
(b) N-methyl-4-amino-hydroxybutylidene-1,1-bisphosphonic acid,
(c) 4-(N,N-dimethylamino-1-hydroxybutylidene-1,1-bisphosphonic acid,
(d) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid,
(e) 3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid,
(f) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid,
(g) 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid, and
(h) 4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine; and

(3) the antiestrogenic compound is selected from:
(a) raloxifene,
(b) clomiphene,
(c) zuclomiphene,
(d) enclomiphene,
(e) nafoxidene,
(f) CI-680,
(g) CI-628,
(h) CN-55,945-27,
(i) Mer-25,
(j) U-11,
(k) 555A, and
(l) U-100A;

and pharmaceutically acceptable salts thereof.

21. The method of treating and preventing a disease involving bone resorption selected from: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease in a subject in need thereof in a subject in need of such treatment according to Claim 20 comprising

8/1/08, EAST Version: 2.2.1.0

administration of 0.01 to 10 mg per day of the 5α-reductase type 2 inhibitor finasteride together with 2.5 to 100 mg/day of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

22. The method according to Claim 12 wherein the bone resorption disease being prevented or treated is osteoporosis.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a therapeutically effective amount of the 5α-reductase type 2 inhibitor finasteride.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a therapeutically effective amount of the 5α-reductase type 2 inhibitor finasteride and a therapeutically effective amount of another agent selected from:

(1) a form of parathyroid hormone,
(2) a growth hormone secretagogue,
(3) growth hormone,
(4) growth hormone releasing hormone,
(5) insulin-like growth factor,
(3) an estrogen,
(4) a bisphosphonate compound, and
(5) an antiestrogenic compound.

25. The pharmaceutical composition according to Claim 24 comprising 0.01 to 10 mg finasteride and 2.5 to 100 mg 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

26. The use of the 5α-reductase type 2 inhibitor finasteride for the preparation of a medicament useful to inhibit bone loss.

27. The use of the 5α-reductase type 2 inhibitor finasteride for the preparation of a medicament useful to prevent or treat

8/1/08, EAST Version: 2.2.1.0

a disease involving bone resorption selected from: osteoporosis, osteopenia, Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease.

28. The use according to Claim 27 of the 5α-reductase type 2 inhibitor finasteride for the preparation of a medicament useful to prevent or treat a disease involving bone resorption selected from: osteoporosis and osteopenia.

8/1/08, EAST Version: 2.2.1.0

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22344

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/56, 31/435, 31, 445
US CL :514/169, 278, 284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/169, 278, 284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS
search terms: finasteride, bone loss, growth hormone secretagogue, spiro, piperidin, indole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,550,134 A (AUDIA ET AL) 27 August 1996, see entire document, especially columns 141-146; columns 151-152, claims 11-24.	1-28
Y	US 5,578,724 A (HAEHL ET AL) 26 November 1996, column 2, lines 50-62; columns 242-246.	1-28
Y	US 5,536,716 A (CHEN ET AL) 16 July 1996, columns 1-9; column 90, claims 8, 9.	8, 18
Y	MOSS et al. Inhibition of human steroid 5-alpha reductase type I and II by 6-aza-steroids: structural determinants of one step vs two step mechanism. Biochemistry. 1996, Vol. 35, No. 11, pages 3457-3464, especially page 3457.	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 27 FEBRUARY 1998	Date of mailing of the international search report 09 APR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*